Asymmetric Michael Additions to α,β-Unsaturated Oxazolines. An Efficient Preparation of Chiral β,β-Disubstituted Propionaldehydes

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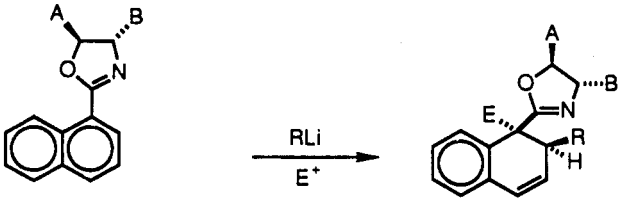
A short stereoselective route to a variety of chiral, nonracemic α,β-unsaturated oxazolines derived from (*S*)-*tert*-leucinol is described. Addition of organolithium reagents to this chiral oxazoline occurs in a Michael fashion, giving rise to adducts with high diastereoselectivity. Reductive cleavage of the oxazoline leaves the β,β-disubstituted aldehydes in >93% ee. This process represents a significant improvement in one of the earliest asymmetric conjugate additions first reported in 1975.

Over the past two decades, the field of asymmetric synthesis has exploded from a mechanistic curiosity to one of the most important areas of organic synthesis.[1] The Michael reaction provides a powerful method of carbon–carbon bond formation; it therefore goes without saying that the development of an asymmetric variant of this reaction is highly desirable. Prior to our report in 1975[2] (Scheme I), there were no meaningful routes to chiral nonracemic Michael addition products; however, in the years following this report, a number of excellent methods were introduced into the literature.[3] As one may have expected, external chiral systems have recently been introduced to effect Michael additions in high stereoselectivity.[4]

From Scheme I it can be seen that complexation of the organolithium to the pendant methoxyl was deemed to be a critical factor in the highly diastereoselective addition observed.[3a] By the same token the substituent, A, was found to be of minimal significance since the diastereoselectivity varied by less than 5% regardless of the nature of A. Recently, we reported that asymmetric conjugate additions to naphthalenes using the chelate-containing oxazoline 1 also proceeded in a diastereoselective fashion. The resulting tandem addition products 3 provided precursors to naturally occurring systems of varying complexity.[5,6] Furthermore, we found that equally efficient



1 A = Ph, B = $MeOCH_2$
2 A = H, B = t-Bu

3

additions of organolithium reagents were possible with the simpler version of the chiral oxazoline 2 providing good yields and de's of 3.[7]

In view of the recent successes utilizing 2, we felt it worthwhile to revisit the process described in Scheme I for several reasons. It was anticipated that the synthesis of α,β-unsaturated oxazolines 7 derived from *tert*-leucinol 4 could be much more efficiently achieved than was previously possible. Furthermore, we had little in the way of smooth removal of the oxazoline in 1975 and required strong acid to convert the addition products in Scheme I to β,β-disubstituted alkanoic acids. In recent years[5-7] we found efficient means to transform the oxazolines into aldehydes, alcohols, and acids.

The sequence depicted in Scheme II was utilized to synthesize a variety of α,β-unsaturated derivatives 7. The oxazoline precursor 5 was prepared in one step by condensation of ethyl acetimidate with (*S*)-*tert*-leucinol (4). Metalation of 5 with lithium diisopropylamide (THF, −78 °C) followed by addition of diethyl chlorophosphate gave phosphonate 6. This crude material was found completely suitable for the subsequent olefination step. Using conditions described by Masamune and Roush[8] for olefination of phosphonates with aldehydes, good yields of 7 were obtained (Table I).[9] The high trans selectivity of this reaction is noteworthy.

With a general route to 7 in hand, we turned our attention to conjugate additions to these chiral electrophilic olefins. Introduction of the oxazolines 7 in THF, to 2.0 equiv of various organolithiums at −78 °C, gave upon quenching with methanol at the same temperature, the 1,4-addition products 8 in good yield (Table II). It should be noted that while conjugate additions proceed smoothly when R = *n*-alkyl, *sec*-alkyl, or aryl, a bulkyl substituent (R = *tert*-butyl) shades the vinyl carbon sufficiently that

(1) The varied works now available describing phenomenal progress in asymmetric synthesis are too many to enumerate here; however, the reader is referred to the following accessible volumes for a survey of major events: (a) Morrison, J. D. *Asymmetric Synthesis*, Vol. 1–5; Academic Press: New York, 1983–1985. (b) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis*; Wiley-Interscience: New York, 1987. (c) Nógrádi, M. *Stereoselective Synthesis*; VCH: 1987.

(2) Meyers, A. I.; Whitten, C. E. *J. Am. Chem. Soc.* **1975**, *97*, 6266. A full account appeared: Meyers, A. I.; Smith, R. K.; Whitten, C. E. *J. Org. Chem.* **1979**, *44*, 2250.

(3) Lutomski, K. A.; Meyers, A. I. Asymmetric Synthesis via Chiral Oxazolines in *Asymmetric Synthesis*, Vol. 3; Academic Press: New York, 1984; p 213. In the same series, descriptions of efficient asymmetric Michael additions are reported: Tomioka, K.; Koga, K. Additions to α,β-Unsaturated Carbonyl Compounds, Vol. 2; p 201. Posner, G. H. Additions of Organometallic Reagents to Chiral Vinyl Sulfoxides, Vol. 2; p 225. Additional examples of asymmetric Michael additions can be found in ref 1c above, pp 221–228. For more recent examples, see: Corey, E. J.; Peterson, R. T. *Tetrahedron Lett.* **1985**, *26*, 5025. Conn, R. S. E.; Lovell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem.* **1986**, *51*, 4710. Davies, S. G.; Dordor-Hedgecock, I. M.; Sutton, K. H.; Walker, J. C. *Tetrahedron Lett.* **1986**, *27*, 3787. Posner, G. H. *Acc. Chem. Res.* **1987**, *20*, 72. Hirai, Y.; Terada, T.; Yamazaki, T. *J. Am. Chem. Soc.* **1988**, *110*, 958. Schöllkopf, U.; Pettig, D.; Schulze, E.; Klinge, M.; Egert, E.; Benecke, B.; Noltemeyer, M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1194. Oppolzer, W.; Kingma, A. J.; Poli, G. *Tetrahedron* **1989**, *45*, 479. Enders, D.; Gerdes, P.; Kipphardt, H. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 179. Dumas, F.; d'Angelo, J. *Tetrahedron Asymm.* **1990**, *1*, 167. Jianguo, C.; Lingchong, Y. *Synth. Commun.* **1990**, *20*, 2887. Haynes, R. K.; Stokes, J. P.; Hambley, T. W. *J. Chem. Soc., Chem. Commun.* **1991**, 58. Schultz, A. G.; Harrington, R. E. *J. Am. Chem. Soc.* **1991**, *113*, 4926.

(4) Tomioka, K. *Synthesis* **1990**, 541.

(5) Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611.

(6) Robichaud, A. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2607.

(7) Rawson, D. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2292.

(8) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(9) Recent studies in our laboratory have established an alternative route to 7 using vinyl halides, and vinyl or aryl triflates, CO, *tert*-leucinol, and palladium catalysts (McKennon, M. J.; Robichaud, A. J.; Meyers, A. I.). This work will be reported in due course.

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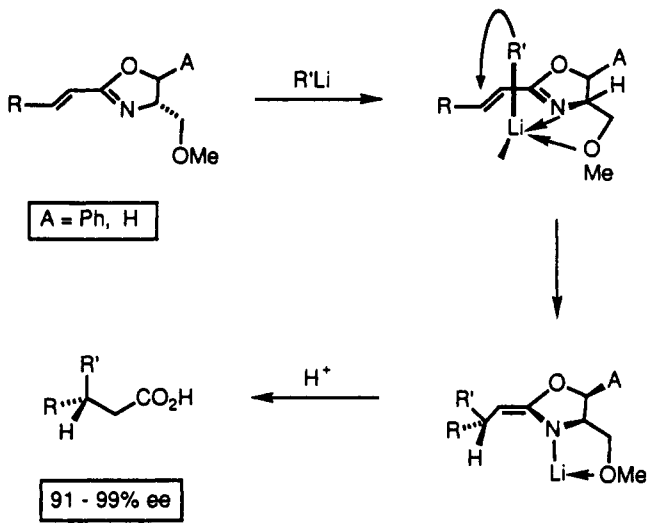
Scheme I



additions are poor. Analysis (NMR) of the crude reaction mixture revealed that all the additions occurred in a highly diastereoselective fashion. Since detection of the minor diastereomer of 8 was not always possible due to its level being below 5%, purification of 8 was bypassed and the crude material was subjected to reductive cleavage to afford pure aldehydic material 9. The enantiomeric purity of the aldehydes was determined by reduction with sodium borohydride to the carbinol 10 and conversion to the Mosher ester[10] 11. ^{19}F and ^{1}H NMR analyses with refer-

Table I. α,β-Unsaturated Oxazolines 7 from 5

oxazoline	R	E:Z[a]	yield, %[b]
7a	*n*-Bu	95:5	73
7b	cyclohexyl	97:3	67
7c	*t*-Bu	100:0	77
7d	Ph	100:0	78
7e		100:0	70

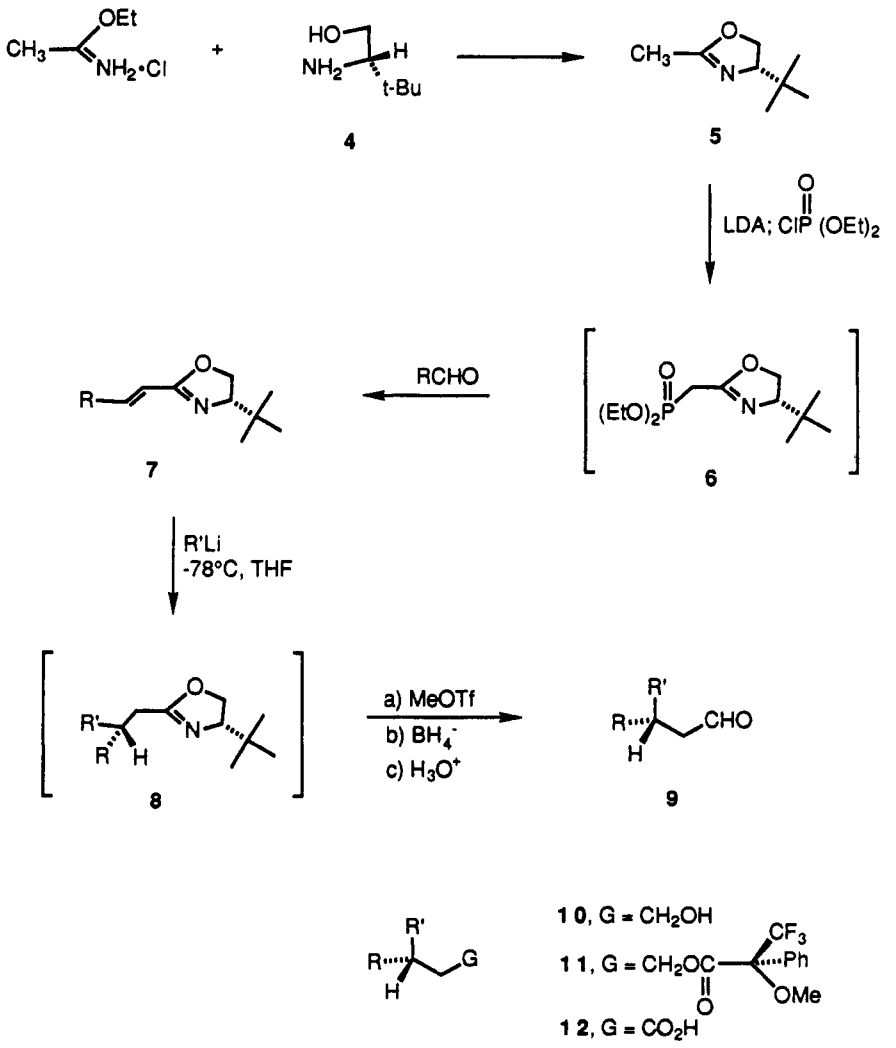
[a] Determined by ^{1}H NMR and/or GLC analyses of the crude reaction mixture. [b] Yield of pure isolated *E* isomer, after chromatography (see Experimental Section).

Table II. Conjugate Additions to Oxazoline 7 To Yield Aldehyde 9

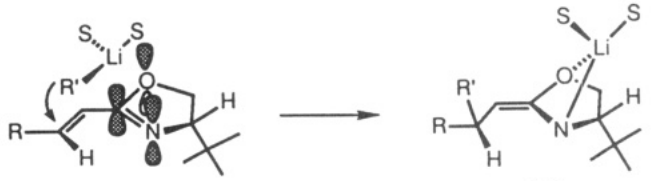
entry	R	R'Li	aldehyde	% yield	confn	% ee[a]
1	*n*-Bu	Ph	**9a**	53	*S*	97[b]
2	cyclohexyl	Ph	**9b**	60	*R*	96[b]
3	Ph	*n*-Bu	**9c**	53	*R*	96[b,c]
4	Ph	*t*-Bu	**9d**	74	*S*	94[b,d]
5		*n*-Bu	**9e**	61	*R*	96[b,d]

[a] The racemic aldehydes were prepared and used for comparison. NMR analyses of Mosher esters derived from carbinol of 9. [b] By ^{1}H NMR analysis of Mosher ester. [c] Enantiomer of entry 1. [d] By ^{19}F NMR analysis of Mosher ester.

Scheme II



ence to racemic material indicated that the enantiomeric excesses of the aldehydes **9** were all greater than 93%. This establishes that the nucleophilic addition to the unsaturated oxazolines proceeds in a highly diastereoselective manner even in the absence of the chelating methoxyl group. The absolute configuration of the aldehydes were established by treating **7** (R = Ph) with *n*-butyllithium, affording **8**. Hydrolysis of the latter using sulfuric acid gave a 96% yield of 3-phenylheptanoic acid **12** with $[\alpha]_D$ = −26.5° (neat). This is in excellent agreement with (*R*)-3-phenylheptanoic acid, $[\alpha]_D$ = −24.9° (neat).[2] Thus, **12** may be written with R′ = *n*-Bu and R = Ph. It should be noted that the sign and magnitude of the optical rotation of (*R*)-**9d** reported in the literature are incorrect.[11] Interestingly, the absolute configuration of the addition products obtained herein is the same as those previously observed in 1975 (Scheme I). The rationale for this sense of stereochemical addition is still considered to be heavily dependent upon complex formation prior to addition. Thus one can consider the organolithium as complexed on the face of the chiral oxazoline made accessible by virtue of the *tert*-butyl group occupying the opposite face, **13**.



13 **14**

The π-orbitals of the oxazoline ring can function as a good Lewis base to the organolithium (either monomeric or polymeric) followed by transfer of the ligand (R′) to the π-system, affording **14** with the observed stereochemistry.[12] This is analogous to additions to naphthalenes, using this same *tert*-leucinol-derived oxazoline.[7]

In summary, returning to one of the first useful asymmetric C–C bond-forming reactions has proven fruitful. With the advantage of 16 years of hindsight and vast improvements in synthetic technology, the asymmetric addition to α,β-unsaturated oxazolines now becomes cleaner, easier, and affords products of high enantiomeric purity.

Experimental Section

General. All reactions were performed in flame-dried glassware under an inert atmosphere. Tetrahydrofuran (THF) was distilled under an atmosphere of argon from sodium–benzophenone ketyl. Methylene chloride and acetonitrile were distilled under argon from calcium hydride. Diethyl chlorophosphate was purchased from the Aldrich Chemical Co. (Milwaukee, WI) and used without further purification. All other solvents and reagents were purified by standard techniques. All organic extracts were dried over $MgSO_4$. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-300 instrument at 300 MHz and 75 MHz, respectively. Carbon multiplicities were established by DEPT experiments.

(4*S*)-4-*tert*-Butyl-2-methyl-2-oxazoline (5). To a stirred solution of ethyl acetimidate hydrochloride[13] (9.6 g, 78 mmol) in methylene chloride (25 mL) at 0 °C was added (*S*)-*tert*-leucinol[14] (7.22 g, 61.6 mmol) in methylene chloride (50 mL). The resulting solution was slowly allowed to warm to room temperature and stirred overnight. The reaction mixture was poured into water (100 mL) and extracted with methylene chloride (3 × 100 mL). The combined organic layers were dried, and the solvent was removed by distillation at atmospheric pressure. Distillation gave **5** (6.23 g, 72%) as a sweet smelling liquid: bp 140–145 °C; $[\alpha]_D$ = −99.7° (*c* 3.0, THF); ^1H NMR ($CDCl_3$) 0.87 (9 H, s), 1.96 (3 H, d, *J* = 1.4 Hz), 3.80 (1 H, m), 3.99 (1 H, t, *J* = 8.3 Hz), 4.13 (1 H, dd, *J* = 10.1, 8.6 Hz); ^{13}C NMR ($CDCl_3$) 13.8 (q), 25.9 (q), 33.5 (s), 68.7 (t), 76.1 (d), 164.3 (s); IR (thin film) 2955, 1681, 1386, 1364, 1229, 984 cm^{-1}; MS, *m*/*e* 141 (M^+), 126 (M^+ − Me), 96, 85.

Preparation of α,β-Unsaturated Oxazolines 7. The following procedure is typical.

(4*S*)-4-*tert*-Butyl-2-((*E*)-1-hexenyl)-2-oxazoline (7a). To a stirred solution of diisopropylamine (4.1 mL, 29 mmol) in THF (20 mL) at 0 °C was added butyllithium (1.7 M in hexanes, 15.6 mL, 26.5 mmol) dropwise. After being stirred for 15 min, the solution was cooled to −78 °C and oxazoline **5** (749 mg, 5.31 mmol) in THF (8 mL) added. The reaction mixture was stirred for 1 h; then diethyl chlorophosphate (0.92 mL, 6.37 mmol) was added. After being stirred for an additional hour, the solution was warmed to 0 °C and the reaction quenched by addition of saturated ammonium chloride solution. The mixture was poured into water, extracted with ether, dried and concentrated to give crude phosphonate **6** (1.71 g) as a yellow oil. This was used directly for the olefination step that follows. To a solution of **6** (1.71 g), lithium chloride (271 mg, 6.39 mmol), and DBU (870 μL, 5.82 mmol) in acetonitrile (40 mL) was added freshly distilled valeraldehyde (680 μL, 6.39 mmol). After being stirred for 16 h, the mixture was poured into water, extracted with methylene chloride, dried ($MgSO_4$), and concentrated. Column chromatography (10–20% EtOAc/hexane) gave **7a** (812 mg, 73%) as a pale yellow liquid: $[\alpha]_D$ = −101° (*c* 2.0, THF); ^1H NMR ($CDCl_3$) 0.90 (12 H, m), 1.25–1.48 (4 H, m), 2.18 (2 H, m), 3.89 (1 H, dd, *J* = 10.0, 8.2 Hz), 4.04 (1 H, t, *J* = 8.2 Hz), 4.18 (1 H, dd, *J* = 10.0, 8.5 Hz), 6.00 (1 H, dt, *J* = 15.9, 1.5 Hz), 6.55 (1 H, dt, *J* = 15.9, 6.9 Hz); ^{13}C NMR ($CDCl_3$) 13.9 (q), 22.2 (t), 25.9 (q), 30.4 (t), 32.3 (t), 33.8 (s), 68.2 (t), 76.0 (d), 117.8 (d), 143.8 (d), 162.8 (s); IR (thin film) 2957, 2872, 1677, 1616, 1358, 998, 986 cm^{-1}; MS, *m*/*e* 209 (M^+), 194 (M^+ − Me), 152 (M^+ − ^{t}Bu), 96. Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.08; N, 6.69. Found: C, 74.23; H, 11.31; N, 6.67.

(4*S*)-4-*tert*-Butyl-2-((*E*)-2-cyclohexylethenyl)-2-oxazoline (7b). Oxazoline **5** (386 mg, 2.73 mmol) in THF (5 mL) was deprotonated with LDA (prepared from butyllithium (8.3 mL, 14.1 mmol) and diisopropylamine (1.57 M in THF, 2.2 mL, 15.7 mmol)), and the reaction was quenched with diethyl chlorophosphate (0.50 mL, 3.46 mmol). The resulting phosphonate **6** (675 mg) was stirred for 42 h with lithium chloride (130 mg, 3.06 mmol), DBU (400 μL, 2.67 mmol), and freshly distilled cyclohexanecarboxaldehyde (350 μL, 2.89 mmol) in acetonitrile (20 mL). Purification by column chromatography (10–20% EtOAc/hexane) gave **7b** (431 mg, 67%) as a clear oil: $[\alpha]_D$ = −94.3° (*c* 1.5, THF); ^1H NMR ($CDCl_3$) 0.90 (9 H, s), 1.05–1.38 (5 H, m), 1.61–1.82 (5 H, m), 2.03–2.17 (1 H, m), 3.90 (1 H, dd, *J* = 10.0, 8.1 Hz), 4.04 (1 H, t, *J* = 8.3 Hz), 4.19 (1 H, dd, *J* = 10.0, 8.4 Hz), 5.96 (1 H, dd, *J* = 16.0, 1.4 Hz), 6.51 (1 H, dd, *J* = 16.0, 6.6 Hz); ^{13}C NMR ($CDCl_3$) 25.9 (t), 26.0 (q), 26.1 (t), 32.0 (t), 33.8 (s), 40.7 (d), 68.2 (t), 76.1 (d), 115.5 (d), 148.8 (d), 163.1 (s); IR (thin film) 2927, 2852, 1674, 1615, 998, 977 cm^{-1}; MS, *m*/*e* 235 (M^+), 178 (M^+ − ^{t}Bu), 137, 96. Anal. Calcd for $C_{15}H_{25}NO$: C, 76.55; H, 10.71; N, 5.95. Found: C, 76.29; H, 10.76; N, 5.87.

(4*S*)-4-*tert*-Butyl-2-((*E*)-3,3-dimethylbutenyl)-2-oxazoline (7c). Oxazoline **5** (920 mg, 6.52 mmol) in THF (10 mL) was deprotonated with LDA (prepared from butyllithium (19.2 mL, 32.6 mmol) and diisopropylamine (1.44 M in THF, 5.0 mL, 36 mmol)), and the reaction was quenched with diethyl chloro-

(10) Prepared according to the procedure described by Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(11) Berlan et al. (Berlan, J.; Besace, Y.; Pourcelot, G.; Creson, P. *Tetrahedron* **1986**, *42*, 4757) report an optical rotation for (*R*)-**9d** (48% ee) $[\alpha]_D$ = −20.3° (*c* 0.1, EtOH). In contrast, the material we prepared (*S*)-**9d** (94% ee) gave an optical rotation $[\alpha]_D$ = −25.8° (*c* 1.0, EtOH). This discrepancy arises from a typographical error in an earlier paper by Almy, J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 4459. In this paper, structures (+)-II-*h*, (−)-VI-*h*, and (+)-V-*h* are correctly drawn with the R configuration but are assigned the *S* stereochemistry.

(12) A referee has suggested that additions to both methoxymethyl- and *tert*-butyl-substituted oxazolines may proceed via the same mechanism. Thus, the organolithium species complexes to the nitrogen atom and the alkyl group is subsequently delivered to the top face of the π-system, anti to the bulky methoxymethyl or *tert*-butyl substituent. Although the authors have also considered this possibility, insufficient evidence is presently available to distinguish between these mechanisms.

(13) *Organic Syntheses*; Wiley: New York, 1941; Collect. Vol. I, p 5.

(14) Obtained by reduction of (*S*)-*tert*-leucine (DeGussa) using the procedure described by Giannis, A.; Sandhoff, K. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 218.

phosphate (1.13 mL, 7.82 mmol). The resulting phosphonate **6** (1.81 g) was stirred for 16 h with lithium chloride (335 mg, 7.90 mmol), DBU (1.07 mL, 7.15 mmol), and freshly distilled pivaldehyde (860 μL, 7.92 mmol) in acetonitrile (50 mL). Purification by column chromatography (20% EtOAc/hexane) gave **7c** (1.05 g, 77%) as a white solid: mp 41–43 °C; $[\alpha]_D$ = −120° (*c* 1.0, THF); ^{1}H NMR ($CDCl_3$) 0.89 (9 H, s), 1.05 (9 H, s), 3.89 (1 H, dd, *J* = 9.9, 8.3 Hz), 4.02 (1 H, t, *J* = 8.3 Hz), 4.20 (1 H, dd, *J* = 9.9, 8.6 Hz), 5.96 (1 H, d, *J* = 16.1 Hz), 6.57 (1 H, d, *J* = 16.1 Hz); ^{13}C NMR ($CDCl_3$) 26.0 (q), 28.9 (q), 33.8 (s), 68.4 (t), 75.8 (d), 113.2 (d), 154.2 (d), 163.6 (s); IR (thin film) 2957, 1672, 1613, 1001, 979 cm^{-1}; MS, *m/e* 209 (M^+), 194 (M^+ − Me), 152 (M^+ − ^{t}Bu), 124, 57, 41. Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.08; N, 6.69. Found: C, 74.65; H, 11.19; N, 6.76.

(4*S*)-4-*tert*-Butyl-2-((*E*)-2-phenylethenyl)-2-oxazoline (7d). Oxazoline **5** (684 mg, 4.84 mmol) in THF (7 mL) was deprotonated with LDA (prepared from butyllithium (14.2 mL, 24.1 mmol) and diisopropylamine (1.44 M in THF, 3.7 mL, 26 mmol)), and the reaction was quenched with diethyl chlorophosphate (0.90 mL, 6.23 mmol). The resulting phosphonate **6** (1.41 g) was stirred for 16 h with lithium chloride (247 mg, 5.83 mmol), DBU (800 μL, 5.35 mmol), and freshly distilled benzaldehyde (600 μL, 5.90 mmol) in acetonitrile (35 mL). Purification by column chromatography (20% EtOAc/hexane) gave **7d** (861 mg, 78%) as a white crystalline solid: mp 95–96 °C; $[\alpha]_D$ = −86.1° (*c* 1.6, THF); ^{1}H NMR ($CDCl_3$) 0.94 (9 H, s), 3.99 (1 H, dd, *J* = 10.0, 8.1 Hz), 4.13 (1 H, t, *J* = 8.2 Hz), 4.28 (1 H, dd, *J* = 10.1, 8.5 Hz), 6.68 (1 H, d, *J* = 16.3 Hz), 7.26–7.49 (6 H, m); ^{13}C NMR ($CDCl_3$) 26.0 (q), 33.9 (s), 68.4 (t), 76.3 (d), 115.5 (d), 127.5 (d), 128.9 (d), 129.4 (d), 135.4 (s), 139.6 (d), 163.1 (s); IR (thin film) 2958, 1656, 1610, 1352, 974, 758 cm^{-1}; MS, *m/e* 229 (M^+), 172 (M^+ − ^{t}Bu), 144, 115, 103, 77. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.44; H, 8.39; N, 6.05.

(4*S*)-4-*tert*-Butyl-2-[(*E*)-2-(2-methoxyphenyl)ethenyl]-2-oxazoline (7e). Oxazoline **5** (413 mg, 2.92 mmol) in THF (5 mL) was deprotonated with LDA (prepared from butyllithium (8.3 mL, 14.1 mmol) and diisopropylamine (1.57 M in THF, 2.2 mL, 15.7 mmol)), and the reaction was quenched with diethyl chlorophosphate (0.53 mL, 3.67 mmol). The resulting phosphonate **6** (711 mg) was stirred for 42 h with lithium chloride (135 mg, 3.18 mmol), DBU (420 μL, 2.81 mmol), and *o*-methoxybenzaldehyde (418 mg, 3.07 mmol) in acetonitrile (20 mL). Purification by column chromatography (20–40% EtOAc/hexane) gave **7e** (527 mg, 70%) as pale yellow crystalline solid: mp 89–91 °C; $[\alpha]_D$ = −93.7° (*c* 1.6, THF); ^{1}H NMR ($CDCl_3$) 0.94 (9 H, s), 3.87 (3 H, s), 3.98 (1 H, dd, *J* = 10.0, 8.0 Hz), 4.13 (1 H, t, *J* = 8.2 Hz), 4.27 (1 H, dd, *J* = 10.0, 8.5 Hz), 6.78 (1 H, d, *J* = 16.4 Hz), 6.88–6.97 (2 H, m), 7.29 (1 H, m), 7.49 (1 H, dd, *J* = 7.7, 1.5 Hz), 7.63 (1 H, d, *J* = 16.4 Hz); ^{13}C NMR ($CDCl_3$) 26.0 (q), 33.9 (s), 55.5 (q), 68.3 (t), 76.3 (d), 111.1 (d), 116.1 (d), 120.8 (d), 124.4 (s), 128.2 (d), 130.5 (d), 134.9 (d), 157.9 (s), 163.7 (s); IR (thin film) 2956, 1657, 1648, 1488, 1248, 983 cm^{-1}; MS, *m/e* 259 (M^+), 228, 202 (M^+ − ^{t}Bu), 174, 145, 115. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.98; H, 8.19; N, 5.37.

Organolithium Additions to α,β-Unsaturated Oxazolines 7 and Subsequent Reductive Hydrolysis to Aldehydes 9a–e. The following procedure is typical.

(3*S*)-3-Phenylheptanal (9a). To a stirred solution of phenyllithium (1.9 M, 0.50 mL, 0.94 mmol) in THF (7.5 mL) at −78 °C was added oxazoline **7a** (93.4 mg, 0.446 mmol) in THF (1.5 mL) dropwise over 30 min. After being stirred for an additional 15 min, the yellow solution was quenched by addition of methanol (1 mL) and subsequently allowed to warm to room temperature. The reaction mixture was poured into water and extracted with ether (3×). The combined organic layers were dried and concentrated. To the crude oxazoline **8** (128 mg) in methylene chloride (2 mL) was added methyl triflate (100 μL, 0.88 mmol). After 1 h, the mixture was cooled to 0 °C and sodium borohydride (56.6 mg, 1.50 mmol) in THF (3 mL) and methanol (1.5 mL) were added via cannula. After a further 30 min, the solution was warmed to room temperature, diluted with water, and extracted with methylene chloride. The combined organic layers were dried and concentrated. Column chromatography (5–8% EtOAc/hexane) gave **9a** (45.3 mg, 53%) as a clear oil: $[\alpha]_D$ = 10.7° (*c* 2.0, C_6H_6); ^{1}H NMR ($CDCl_3$) 0.83 (3 H, t, *J* = 7.4 Hz), 1.06–1.35 (4 H, m), 1.55–1.70 (2 H, m), 2.71 (2 H, dd, *J* = 7.2, 1.5 Hz), 3.11–3.21 (1 H, m), 7.17–7.33 (5 H, m), 9.66 (1 H, t, *J* = 2.1 Hz); ^{13}C NMR ($CDCl_3$) 14.0 (q), 22.6 (t), 29.5 (t), 36.4 (t), 40.2 (d), 50.7 (t), 126.6 (d), 127.5 (d), 128.7 (d), 144.1 (s), 202.1 (d); IR (thin film) 2957, 2929, 1725, 1454, 701 cm^{-1}; MS, *m/e* 190 (M^+), 172, 133, 105, 91. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 81.82; H, 9.53.

(3*R*)-3-Cyclohexyl-3-phenylpropanal (9b). Oxazoline **7b** (108 mg, 0.458 mmol) in THF (1.5 mL) was added to phenyllithium (1.9 M, 0.49 mL, 0.921 mmol) in THF (7.5 mL). The crude adduct **8** in methylene chloride (2 mL) was stirred for 2.5 h with methyl triflate (110 μL, 0.97 mmol) and then treated with sodium borohydride (51.9 mg, 1.37 mmol) in THF (3 mL) and methanol (0.75 mL) for 1 h. The resulting oxazolidine was stirred with oxalic acid dihydrate (295 mg, 2.34 mmol) for 48 h. Purification by column chromatography (5–8% EtOAc/hexane) gave **9b** (59.8 mg, 60%) as a clear oil: $[\alpha]_D$ = −0.6° (*c* 2.5, C_6H_6); ^{1}H NMR ($CDCl_3$) 0.74–1.31 (5 H, m), 1.42–1.86 (6 H, m), 2.71 (1 H, ddd, *J* = 16.4, 9.5, 2.5 Hz), 2.83 (1 H, ddd, *J* = 16.4, 5.4, 1.9 Hz), 2.93–3.02 (1 H, m), 7.11–7.31 (5 H, m), 9.60 (1 H, t, *J* = 2.2 Hz); ^{13}C NMR ($CDCl_3$) 26.4 (t), 26.5 (t), 30.8 (t), 31.2 (t), 43.2 (d), 46.3 (d), 47.2 (t), 126.6 (d), 128.36 (d), 128.44 (d), 142.9 (s), 202.6 (d); IR (thin film) 2924, 2852, 1725, 1450, 702 cm^{-1}; MS, *m/e* 216 (M^+), 172, 134, 105, 92, 91, 55. Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.17; H, 9.49.

(3*R*)-3-Phenylheptanal (9c). Oxazoline **7d** (92.2 mg, 0.402 mmol) in THF (1.5 mL) was added to butyllithium (1.7 M, 0.47 mL, 0.80 mmol) in THF (6.5 mL). The crude adduct in methylene chloride (2 mL) was stirred for 2.5 h with methyl triflate (100 μL, 0.88 mmol) and then treated with sodium borohydride (46.7 mg, 1.23 mmol) in THF (3 mL) and methanol (0.75 mL) for 1 h. The resulting oxazolidine was stirred with oxalic acid dihydrate (253 mg, 2.01 mmol) for 44 h. Purification by column chromatography (5–8% EtOAc/hexane) gave **9c** (44.1 mg, 53%) as a clear oil: $[\alpha]_D$ = −11.1° (*c* 2.2, C_6H_6); other spectral data identical to 3S enantiomer **9a**.

(3*S*)-4,4-Dimethyl-3-phenylpentanal (9d).[11] Oxazoline **7d** (101 mg, 0.442 mmol) in THF (1.5 mL) was added to *tert*-butyllithium (1.6 M, 0.56 mL, 0.90 mmol) in THF (7.5 mL). The crude adduct in methylene chloride (2 mL) was stirred for 2.5 h with methyl triflate (100 μL, 0.88 mmol) and then treated with sodium borohydride (50.9 mg, 1.34 mmol) in THF (3 mL) and methanol (0.75 mL) for 1 h. The resulting oxazolidine was stirred with oxalic acid dihydrate (280 mg, 2.22 mmol) for 48 h. Purification by column chromatography (5–8% EtOAc/hexane) gave **9d** (62.0 mg, 74%) as a clear oil: $[\alpha]_D$ = −37.1° (*c* 3.0, C_6H_6); ^{1}H NMR ($CDCl_3$) 1.09 (9 H, s), 2.45 (1 H, ddd, *J* = 11.0, 3.7, 3.1 Hz), 2.83 (1 H, dd, *J* = 14.0, 2.9 Hz), 3.03 (1 H, dd, *J* = 14.0, 11.1 Hz), 7.11–7.27 (5 H, m), 9.75 (1 H, d, *J* = 3.9 Hz); ^{13}C NMR ($CDCl_3$) 28.1 (q), 31.1 (t), 34.0 (s), 63.8 (d), 126.2 (d), 128.6 (d), 128.9 (d), 140.0 (s), 205.7 (d); IR (thin film) 2963, 1724, 1370, 699 cm^{-1}; MS, *m/e* 190 (M^+), 133 (M^+ − ^{t}Bu), 115, 105, 91, 57. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 82.07; H, 9.72.

(3*R*)-3-(2-Methoxyphenyl)heptanal (9e). Oxazoline **7e** (102 mg, 0.394 mmol) in THF (1.5 mL) was added to butyllithium (1.7 M, 0.49 mL, 0.83 mmol) in THF (6.5 mL). The crude adduct in methylene chloride (2 mL) was stirred for 2.5 h with methyl triflate (90 μL, 0.80 mmol) and then treated with sodium borohydride (43.4 mg, 1.15 mmol) in THF (3 mL) and methanol (0.75 mL) for 1 h. The resulting oxazolidine was stirred with oxalic acid dihydrate (247 mg, 1.96 mmol) for 44 h. Purification by column chromatography (5–8% EtOAc/hexane) gave **9e** (52.9 mg, 61%) as a clear oil: $[\alpha]_D$ = −10.1° (*c* 1.4, C_6H_6); ^{1}H NMR ($CDCl_3$) 0.84 (3 H, t, *J* = 7.1 Hz), 1.08–1.35 (4 H, m), 1.56–1.77 (2 H, m), 2.66 (2 H, dd, *J* = 7.3, 2.4 Hz), 3.56–3.65 (1 H, m), 3.82 (3 H, s), 6.85–6.94 (2 H, m), 7.12–7.22 (2 H, m), 9.64 (1 H, t, *J* = 2.4 Hz); ^{13}C NMR ($CDCl_3$) 14.0 (q), 22.7 (t), 29.6 (t), 33.4 (d), 34.7 (t), 49.6 (t), 55.3 (q), 110.8 (d), 120.8 (d), 127.4 (d), 127.9 (d), 131.9 (s), 157.2 (s), 203.0 (d); IR (thin film) 2956, 2930, 1724, 1493, 1241 cm^{-1}; MS, *m/e* 220 (M^+), 177, 163, 135, 121, 91. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.41; H, 9.12.

(3*R*)-3-Phenylheptanoic Acid (12, R = Ph, R′ = *n*-Bu).[2] To a stirred solution of butyllithium (1.7 M, 13.0 mL, 22.1 mmol)

in THF (150 mL) at -78 °C was added oxazoline **7d** (2.40 g, 10.5 mmol) in THF (60 mL) dropwise over 75 min. After being stirred for an additional 15 min, the orange solution was quenched by addition of methanol (20 mL) and subsequently allowed to warm to room temperature. The reaction mixture was poured into water and extracted with ether. The combined organic layers were dried and concentrated. The resulting oxazoline **8** (3.07 g) was refluxed with sulfuric acid (1.8 M, 150 mL) for 40 h. On cooling, the mixture was extracted with methylene chloride, dried, and concentrated. Bulb-to-bulb distillation yielded **12** (2.07 g, 96%) as a viscous oil: bp 150 °C/0.3 mmHg; $[\alpha]_D$ = -26.5° (neat); ^{1}H NMR ($CDCl_3$) 0.82 (3 H, t, J = 7.1 Hz), 1.05-1.31 (4 H, m), 1.56-1.68 (2 H, m), 2.59 (1 H, dd, J = 15.5, 7.9 Hz), 2.66 (1 H, dd, J = 15.5, 7.1 Hz), 3.06 (1 H, m), 7.15-7.32 (5 H, m), 11.30 (1 H, br s); ^{13}C NMR ($CDCl_3$) 14.0 (q), 22.6 (t), 29.5 (t), 36.0 (t), 41.6 (t), 41.9 (d), 126.6 (d), 127.5 (d), 128.5 (d), 144.0 (s), 178.7 (s); IR (thin film) 3400-2500, 2958, 2930, 1709, 1454 cm^{-1}.

Determination of Enantiomeric Excesses of Aldehydes 9. To the aldehyde **9** (10-20 mg) in methanol (1 mL) at 0 °C was added excess sodium borohydride. After being stirred for 15 min, the solution was warmed to room temperature, diluted with water, and extracted with methylene chloride. The combined organic layers were dried and concentrated. The resulting alcohol **10** was converted to the Mosher's ester according to a published procedure using (*S*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid.[10] NMR analysis was performed on base-line resolved signals as ascertained by comparison with the corresponding materials derived from the racemic aldehydes.[15] In all cases, benzene-d_6 was employed as solvent. The following resonances were employed: For diastereomeric materials (**11a** and **11c**) the signals at δ = 3.83 (1 H) and 4.09 (1 H) were integrated relative to that at δ = 3.94 (2 H); for **11b** the signals at δ = 3.76 (1 H) and 4.11 (1 H) were integrated relative to the signals observed in the racemic material at δ = 3.76 (0.5 H), 3.87 (0.5 H), 3.98 (0.5 H), and 4.11 (0.5 H); for **11d** the singlet at δ = 0.74 (9 H) was integrated relative to the two singlets observed for the racemic material at δ = 0.78 (4.5 H) and 0.74 (4.5 H), also by integration of the singlet at δ = -43.48 relative to those observed for the racemic material at δ = -43.48 and -43.66 in the ^{19}F NMR (188 MHz); for **11e** the signal at δ = 3.40 (3 H) was integrated relative to the two signals observed for the racemic material at δ = 3.40 (1.5 H) and 3.44 (1.5 H), also by integration of the singlet at δ = -43.03 relative to those observed for the racemic material at δ = -43.03 and -43.09 in the ^{19}F NMR.

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(15) Prepared in an analogous fashion utilizing 2,4,4-trimethyl-2-oxazoline.

Multiarmed Macrocyclic Polyamines Exhibiting Unique Cation-Binding and Cation-Transport Properties toward Alkali-Metal and Alkaline-Earth-Metal Cations

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A variety of multiarmed macrocyclic polyamines were prepared as a new type of metal carrier, in which amide-, ester-, nitrile-, and ketone-functionalized arms were attached as secondary donor sites. Extraction and ^{13}C NMR binding experiments revealed that their cation-binding behavior was largely dependent on the nature of the arm donor group as well as the size of the parent polyamine ring. In particular, introduction of an amide-functionalized arm into a suitable polyamine ring significantly enhanced binding ability toward "hard" metal cations, while the parent polyamine ring weakly bound these metal cations. Their unique cation-binding properties offered an effective membrane transport of hard metal cations. Since the cation-binding and -transport profiles of the new multiarmed macrocyclic polyamines differed greatly from those observed with conventional polyamines and related macrocycles, the present study provides a new possibility for designing a novel, macrocyclic polyamine type of synthetic carrier.

Introduction

Lariat ethers, double-armed crown ethers, and related macrocyclic host molecules have attracted much attention, and all are characterized by parent macrocyclic ligands and flexible cation-ligating arm groups.[1] They form three-dimensional and stable metal complexes via side-arm-macroring cooperativity. Since the rates of formation and dissociation of their metal complexes are often modified by the incorporation of pendant arms, compounds of this class can act as unique carriers of various metal cations.[2] Interestingly, their cation-binding and -transport properties are essentially controlled by the natures of the macrocyclic skeleton and ligating side arm, and we are able to select a structural combination suitable for a new and specific carrier of a target guest cation.

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